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(54) Title: ORAL CARE COMPOSITIONS		
(57) Abstract		
<p>The invention relates to an oral care composition with antiplaque agents. The antiplaque agents are complexes of divalent copper, zinc, iron or tin, or trivalent iron with a specific class of cyclic α-hydroxyketones. A typical example is the copper(II)-ethylmaltol complex. These complexes are more active antiplaque agents than e.g. copper-hinokitiol complexes.</p>		

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"Oral Care Compositions"

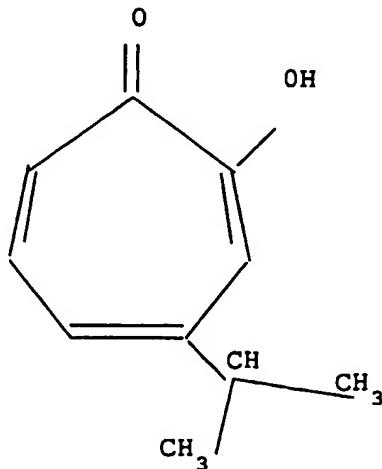
The present invention relates to oral care compositions comprising particular antiplaque agents. More particularly, it relates to oral care compositions comprising certain copper, zinc, iron or tin metal complexes comprising biologically active ligands as antiplaque agents.

It is already known, that copper and zinc metals complexes comprising certain biologically active ligands have an antimicrobial activity. Thus, for example, in EP-A-0728478 (Otsuka Pharmaceutical Co., Ltd.), copper-hinokitiol and zinc-hinokitiol complexes are described, which are stated to have antimicrobial activity. According to this publication, these copper- and zinc-hinokitiol complexes can be usefully included in oral care compositions.

Hinokitiol is 4-isopropyl tropolone, a cyclic α -hydroxyketone having the structure

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We have now found that a different class of cyclic α -

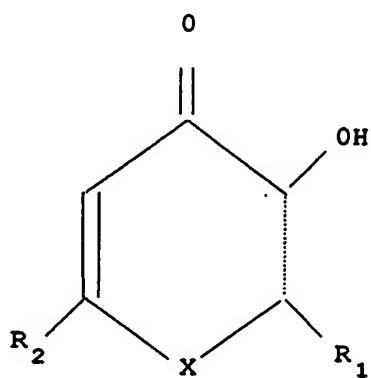
hydroxyketones are biologically active ligands, capable of forming complexes with copper, zinc, iron and tin, said complexes

having an antiplaque activity which is superior to the 5 aforementioned copper- and zinc-hinokitiol complexes.

The class of cyclic α -hydroxyketones according to the present invention is represented by the following general structural formula:

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20 in which X represents 0 or NR₃, R₁ and R₃ represent H or a C₁-C₁₆, preferably a C₁-C₄ branched or straight-chain alkylgroup, and R₂ represents H or a hydroxymethylgroup.

The link between the carbon atoms in the ring structure at positions 2 and 3 can be saturated or unsaturated, and is 25 preferably unsaturated.

This class of cyclized α -hydroxyketones embraces, therefore, derivatives of hydroxypyran-4-ones and hydroxypyridin-4-ones. Typical examples of these cyclic α -hydroxyketones are 30 maltol (= 3-hydroxy-2-methyl-4H-pyran-4-one), X being 0, R₁ being methyl and R₂ being H; ethylmaltol (3-hydroxy-2-ethyl-4H-pyran-4-one), X being 0, R₁ being ethyl and R₂ being H; kojic acid (5-hydroxy-2-(hydroxymethyl)-4H-pyran-

4-one), X being 0, R₁ being H and R₂ being hydroxymethyl; 2-methyl-3-hydroxypyridin-4-one, X = NR₃, R₃ = H, R₁ = methyl and R₂ = H; 1,2-dimethyl-3-hydroxypyridin-4-one, X = NR₃, R₃ = methyl, R₁ = methyl and R₂ = H; and 1-ethyl-2-5 methyl-3-hydroxypyridin-4-one, X = NR₃, R₃ = ethyl, R₁ = methyl and R₂ = H.

The metals which are complexed by the above class of cyclic α-hydroxyketones are divalent copper, zinc, iron and tin
10 and trivalent iron.

The cyclic α-hydroxyketones of the present invention, and the metal complexes thereof, are known in the art and can be synthesised by established methodologies, as e.g.
15 described in Acta Cryst. B32 (1976) page 3121 by Berg, et al., in Can. J. Chem. 68, (1990) page 1598 by Annan, et al., J. Chem. Soc., Dalton Trans. (1992) page 2375 by Denekamp, et al., in J. Med. Chem. 37 (1994) page 461 by El-Jammal, et al., and in J. Med. Chem. 39 (1996) page 3659 by
20 Ellis, et al.. Suitable complexes can be formed from a suitable divalent copper, zinc, iron or stannous salt or a trivalent iron salt with the cyclic α-hydroxyketones in molar ratios of between 10:1 to 1:10, preferably 4:1 to 1:4, particularly preferably 2:1 to 1:2 (the molar ratio
25 being calculated on the basis of the metal ion).

The preferred metal complexes according to the present invention are the Cu²⁺ and Sn²⁺ complexes, particularly the Cu²⁺- and Sn²⁺ maltol and -ethylmaltol complexes.

30

The metal complexes of the present invention are included in the oral care compositions in an amount, ranging from 0.001 to 5 % by weight of the composition, preferably 0.1

to 3 % by weight, and optimum results are obtained with amounts, ranging from 0.2 to 2 by weight of the composition. Mixtures of the various metal complexes may also be used. The complexes may be prepared prior to their incorporation in the oral care composition, or they may be prepared in situ during the manufacture of the oral care composition. It may sometimes be advantageous to use an amount of the cyclic α -hydroxyketone, in excess of the stoichiometric equivalent, required for the formation of the complex, to prevent possible decomposition of the complexes in the oral care composition during storage, and to possibly further increase the antiplaque activity of the complexes. It has also been found that it is sometimes advantageous to use an excess of the metal salt, e.g. the copper or stannous salt, to further increase the antiplaque activity.

The oral care compositions of the present invention may furthermore comprise optional, conventional ingredients such as pharmaceutically acceptable carriers like starch, sucrose, water or water/alcohol systems etc.. Small amounts of surfactants may also be included, such as anionic, nonionic, cationic and zwitterionic or amphoteric surfactants. They may comprise particulate abrasive materials such as silicas, aluminas, calcium carbonates, dicalciumphosphates, calcium pyrophosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, including agglomerated particulate abrasive materials, usually in amounts between 3 and 60% by weight. In the case of calcium carbonates being used as the abrasive materials, the metal complexes of the present invention are more compatible with such materials than other metal salts, e.g. copper salts, which

are according to EP-B-38867 (Blendax) rather incompatible with calcium carbonates.

Furthermore, they may comprise humectants such as glycerol,
5 sorbitol, propyleneglycol, xylitol, lactitol and so on.

Binders and thickeners such as sodium carboxymethyl-cellulose, xanthan gum, gum arabic etc. may also be included, as well as synthetic polymers such as
10 polyacrylates and carboxyvinyl polymers such as Carbopol®.

Flavours such as peppermint and spearmint oils may also be included, as well as preservatives, opacifying agents, colouring agents, pH-adjusting agents, sweetening agents
15 and so on.

Additional anti-bacterial agents may also be included such as Triclosan, chlorhexidine, copper-, zinc- and stannous salts such as zinc citrate, sodium zinc citrate and
20 stannous pyrophosphate, sanguinarine extract, metronidazole. Further examples of anti-bacterial agents are quaternary ammonium compounds such as cetylpyridinium chloride; bis-guanides such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; halogenated bisphenolic
25 compounds such as 2,2' methylenebis-(4-chloro-6-bromophenol).

Polymeric compounds which can enhance the delivery of active ingredients such as anti-bacterial agents can also
30 be included. Examples of such polymers are copolymers of polyvinylmethylether with maleic anhydride and other similar delivery enhancing polymers, e.g. those described in DE-A-3,942,643 (Colgate)

While the complexes of the present invention are particularly useful as anti-plaque agents, they are also useful as antimicrobial- and anti-gingivitis agents in oral
5 care products.

Furthermore anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin etc. may also be included.

10

Anti-caries agents such as sodium- and stannous fluoride, aminefluorides, sodium monofluorophosphate, casein, plaque buffers such as urea, calcium lactate, calcium glycerophosphate, strontium polyacrylates may also be included. Other optional ingredients include vitamins such as Vitamin C, and plant extracts. Desensitizing agents such as glycerolmonooleate potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, potassium nitrate as well as strontium salts may also be included.
15
20

Buffers and salts to buffer the pH and ionic strength of the compositions may also be included. Liposomes and other encapsulates may also be used to improve delivery or
25 stability of active ingredients.

Furthermore, the oral compositions may comprise anti-calculus agents such as alkali metal pyrophosphates, hypophosphite-containing polymers, organic phosphonates,
30 phosphocitrates etc..

In addition, the compositions may comprise functional biomolecules such as bacteriocins, antibodies, enzymes and

so on.

Other optional ingredients that may be included are e.g. bleaching agents such as peroxy compounds e.g. potassium 5 peroxydiphosphate, effervescent systems such as sodium bicarbonate/citric acid systems, colour change systems, and so on.

The toothpastes may also be formulated into systems for use
10 in dual-compartment type dispensers.

The present invention will be further illustrated by way of Example.

Example 1

In vitro biofilm antiplaque tests were carried out with copper salts, and copper complexes of hinokitiol and 5 maltol.

The test is based on monitoring the growth (by measuring absorbance) of a biofilm of a single species of bacteria, formed in the wells of a 96 well plate, after treatment 10 with toothpaste slurries, and calculating the time taken to reach a chosen turbidity (i.e. a chosen absorbance value at 630nm)

A sample of *S. warneri* was cultured overnight in BHI 15 medium. The culture was centrifuged and washed twice with phosphate-buffered saline (PBS) to an approximate optical density of 1.0. A 200 µl aliquot of bacterial suspension was pipetted into wells of a maleic anhydride-activated polystyrene 96-well plate (Pierce-Warriner, Chester). 20 Plates were covered with a sterile plate sealer (to prevent contamination), centrifuged (3000 rpm, 4 minutes) and incubated for 1 hour at 37°C. Plates were used on the day of preparation, and were kept until use at room temperature, or if not required for several hours, at 4°C. 25 Biofilm-coated wells were washed three times with PBS taking care to avoid disrupting the bacteria.

Toothpaste slurries were prepared by mixing paste with water to give 33% (w/w) slurries and centrifuging for 10 or 30 20 minutes at 3,500 rpm (Heraeus Labofuge 400 or MSE Mistral 1000 centrifuge). The supernatant was decanted into sterile containers and used within a day.

After washing plates, wells were treated with 200 µl of toothpaste supernatant for 30 seconds. Plates were inverted over a beaker of Virkon sterilizing solution, dried by patting down on absorbent paper, washed three 5 times with sterile Milli-Q grade and dried by patting down on absorbent paper.

After treatment and washing, 200 µl of BHI followed by 80 µl of sterile light mineral oil was added to each well. 10 Plates were incubated at 37°C in a microtitre plate reader (Dynex Technologies DIAS) and growth monitored at 630 nm every 15 minutes for 16 hours. The end-point was taken as the time taken to reach an A_{630} of 0.4. This absorbance approximated to the inflection point of the growth curve 15 for each bacterium, where growth of the culture is most rapid. The point of maximum growth rate was taken as it is the least sensitive to variations in the background absorbance and the most sharply resolved point on the time axis. The time to reach the optical density of 0.4 was 20 recorded. The longer the growth time, the more effective the treatment.

In a conventional toothpaste containing chalk as the abrasive cleaning agent, the following results were 25 obtained:

Time to reach the optical density (O.D.) of 0.4 (in hrs)	% by weight of Cu (as CuSO ₄)	% by weight of maltol
5.32	-	-
5.39	0.1	-
5.14	-	0.1
12.29	0.1	0.1
4.15	-	0.2
10.26	0.1	0.2

These results show, that the copper (II)-maltol complex (formed in situ as evidenced by the formation of a green colour in the paste) has a significantly greater antibacterial effect than either CuSO₄ or maltol alone, as evidenced by the significantly longer periods to reach the O.D. of 0.4

10 Repeating these tests with a conventional toothpaste containing silica as the abrasive agent gave the following results:

Time to reach the (O.D.) of 0.4 (in hrs)	% by weight of Cu (as CuSO ₄)	% by weight of maltol
4.88	-	-
6.20	0.1	-
5.10	-	0.1
13.86	0.1	0.1
4.79	-	0.2
12.92	0.1	0.2

These results also clearly show the superiority of the copper (II)-maltol complex over coppersulphate as antibacterial agent.

5 Repeating these experiments in a model toothpaste solution gave the following results

Time to reach the optical density (O.D.) of 0.4 (in hrs)	% by weight of Cu (as CuSO ₄)	% by weight of maltol
4.34	-	-
6.49	0.1	-
4.38	-	0.1
9.39	0.1	0.1
4.69	-	0.2
9.57	0.1	0.2

10 For comparison, 0.25% of CuSO₄ and 0.25% hinokitiol produced a growth time to reach the O.D. of 0.4 of 7 hrs, 0.25% CuSO₄ alone 4.82 hrs, 0.25% hinokitiol alone 4.54 hrs.

15 Increasing the amounts of maltol, at a level of CuSO₄ of 0.1%, gave the following results in the above model toothpaste solution test

Time to (O.D.) of 0.4 (in hrs)	% by weight of maltol
4.03	--
9.66	0.1
9.72	0.2

12

9.38	0.5
8.55	1

In all the above tests, the copper(II) sulphate was its pentahydrate salt.

5 Similar results are obtained when using the zinc, iron and stannous complexes of maltol and ethylmaltol.

Example 2

10 The following toothpastes were prepared:

PRODUCT _____	1. (PLACEBO)	2.	3.	4.
INGREDIENT				
SORBITOL (70%)	45.00	45.00	45.00	45.00
SODIUM SACCHARIN	0.17	0.17	0.17	0.17
TITANIUM DIOXIDE	1.00	1.00	1.00	1.00
POLYETHYLENE GLYCOL 1500	5.00	5.00	5.00	5.00
THICKENING SILICA	8.00	8.00	8.00	8.00
ABRASIVE SILICA	10.00	10.00	10.00	10.00
CELLULOSE GUM	0.90	0.90	0.90	0.90
SODIUM LAURYL SULPHATE	1.50	1.50	1.50	1.50
FLAVOUR	1.00	1.00	1.00	1.00
COPPER SULPHATE PENTAHYDRATE	-	0.20	0.20	0.20
HINOKITIOL	-	-	0.20	-

ETHYLMALTOL	-	-	-	0.20
ETHANOL	-	-	-	1.0
WATER	TO 100%	TO 100%	TO 100%	TO 100%

5 The plaque inhibition (PGI) by these products was measured according to the plaque growth inhibition test method as described by Harrap in J. Clin. Periodontol (1) (1974) pp. 166-174, using single brushing and product 1 as placebo, and measuring the plaque at the beginning of the test and 10 after 18 hours. The PGI is expressed as a percentage according to the formula:

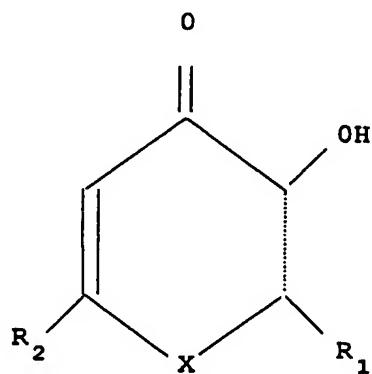
$$15 \quad PGI(\%) = \{ 1 - \frac{PG_{18 \text{ hrs(test)}} - PG_{0 \text{ hrs(test)}}}{PG_{18 \text{ hrs(placebo)}} - PG_{0 \text{ hrs(placebo)}}} \} \times 100$$

Product	PGI(%)	Std. Error	p
2	15.16	11.43	n.s.
3	11.98	12.45	n.s.
4	26.31	10.686	0.026

20 These results show, that the copper(II) ethylmaltol complex has a significantly higher PGI than the placebo, whereas the PGI of copper alone or the copper-hinokitiol complex was not significantly different from the placebo.

Claims

1. An oral care composition comprising a copper-, zinc, iron or stannous compound as antiplaque agent, characterised in that the compound is a complex of divalent copper, zinc, iron or tin, or trivalent iron, bonded to a biologically active ligand which is a cyclic α -hydroxyketone of the following general formula:



in which X represents O or NR₃, R₁ and R₃ represent H or a C₁-C₁₆ branched or straight-chain alkylgroup, and R₂ represents H or a hydroxymethylgroup, the link between the carbon atoms in the ring structure at positions 2 and 3 being saturated or unsaturated.

2. An oral care composition according to claim 1, characterized in that the link is unsaturated.
3. A composition according to claim 1 or 2, characterized in that R₁ and R₃ represent H or a C₁-C₄ branched or straight-chain alkyl group.

4. An oral care composition according to claims 1-3, characterised in that the complex is a divalent copper complex.
5. An oral care composition according to claims 1-4, characterised in that the cyclic α -hydroxyketone is ethylmaltol.
6. The use of complexes of divalent copper, zinc, iron or tin, or trivalent iron, bonded to a cyclic α -hydroxyketone according to the formula of claim 1, as an antimicrobial, antiplaque or anti-gingivitis agent in the manufacture of an oral care composition.

INTERNATIONAL SEARCH REPORT

Inte .onal Application No
PCT/EP 99/07380

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 1 507 846 A (THE PROCTER AND GAMBLE CO.) 19 April 1978 (1978-04-19) claim 1 ---	1,4-6
A	US 5 037 634 A (WILLIAMS, D. R. ET AL.) 6 August 1991 (1991-08-06) column 06; claims 1,6-8 ---	1,4
A	US 5 587 147 A (DOMKE, T. W. ET AL.) 24 December 1996 (1996-12-24) claims 1,5,6 -----	1

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Patent family members are listed in annex.

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Information on patent family members

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